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Catalytic bioscavengers against organophosphorus agents: mechanistic issues of self-reactivating cholinesterases

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ABSTRACT

Catalytic bioscavengers are the second-generation bioscavengers. These biopharmaceuticals are intended to degrade toxic organophosphorus agents on the skin for decontamination or in the bloodstream for pre-treatment and post-exposure treatment of organophosphate poisoning. Because catalytic degradation has to be fast, their catalytic efficiency has to be as high as possible ($k_{cat}/K_m > 10^6\ M^{-1}\,min^{-1}$). Certain evolved mammalian paraoxonases and bacterial phosphotriesterases already fulfill this requirement.

To be of interest, the catalytic activity of certain enzymes has to be increased by several orders of magnitude. This can be reached by computer-redesign or directed evolution existing enzymes, and alternatively, combinational strategies.

The present paper focuses on the better understanding of catalytic mechanisms of cholinesterase inhibition, aging and reactivation and how this knowledge serves the rational design of novel catalytic bioscavengers based on cholinesterase structure.

1. Introduction

Limitations and multiple difficulties of current pretreatment and post-exposure treatment of OP poisoning (Masson, 2016) have stimulated scientists to research alternative approaches to classical pharmacological drugs. The idea of scavenging and neutralizing OP molecules before they reach physiological targets progressively has emerged in the 80 s. Some 30 years ago, the basic concepts of the bioscavenger approach were already well established.

Three classes of bioscavengers can be defined: a) stoichiometric bioscavengers that react mole-to-mole with OPs in a suicide reaction, b) catalytic bioscavengers that react with a turnover with substrate OPs, c) pseudo-catalytic bioscavengers are stoichiometric bioscavengers assisted of nucleophilic molecules (oximates) that displace the phosphyl moiety, thus creating a pseudo-turnover. Several recent reviews were devoted to the different types of bioscavengers and their use with conventional medical countermeasures (Satvik Iyengar et al., 2015; Worek et al., 2016; Masson and Lushchekina, 2016; Masson and Nachon, 2017; Goldsmith and Ashani, 2018). Requirements needed to develop biopharmaceuticals of interest (bimolecular rate of reaction with OPs, production under GMP conditions, delivery systems, capping and encapsulation, pharmacokinetics, absence of side effects, immunocompatibility and economic issues) have been discussed in above-cited reviews. The present paper focuses on the basic knowledge needed to design ChE-based catalytic bioscavengers capable of degrading OPs with high efficiency.

2. Bioscavengers

Mandatory kinetic requirements determine the operational interest of bioscavengers. Reaction between OP molecules and bioscavengers has to be fast to prevent transfer of toxicant to targets. Moreover, because of narrow specificity and enantioselectivity, mixtures of bioscavengers must be administered to cover the whole spectrum of existing OPs. In addition, bioscavengers must be stable, have a slow clearance in the bloodstream, and they must not induce iatrogenic effects. Encapsulation into nanocontainers or chemical capping may prevent immune response and fast elimination.

Abbreviations: AChE, acetylcholinesterase; BChE, butyrylcholinesterase; ChEs, cholinesterases; CWA, chemical warfare agents; CWNA, chemical warfare nerve agent; EI, enzyme-inhibitor conjugate; EVB, empirical valence bond; FE, free energy; MD, molecular dynamics; NA, nerve agent; OP, organophosphorus compound; OPase, organophosphate hydrolase; PLL, phosphotriesterase-like lactonase; PON, paraoxonase; PTE, phosphotriesterase; QM/MM, quantum mechanics/molecular mechanics; TS, transition state

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